Neuroradiological and neurofunctional examinations for the patients with 22q11.2 deletion

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Abbreviations

MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
IMZ	iomazenil
SPECT	single photon emission computed tomography
EEG	electroencephalogram
GABA	γ -aminobutyric acid
MRA	magnetic resonance angiography
PRESS	Point Resolved Spectroscopy
CHESS	chemical shift-selective
TR	repetition time
TE	echo time
ROI	region of interest
NAA	N-acetyl aspartate
Glu	glutamate
%SD	percent standard deviation
STEAM	stimulated echo acquisition mode
Cr	creatinine
mIns	myo-inositol
Cho	choline-containing compoundsSubjects

・Abstract

Since neuroradiological features of patients with 22q11.2 deletion syndrome are not well-understood, examinations using functional imaging were performed in this study.

Brain magnetic resonance imaging(MRI) and ^{1}H-magnetic resonance spectroscopy(MRS) were performed using a clinical 3-tesla MR imager in 4 patients with 22q11.2 deletion syndrome (2 boys and 2 girls; 2~6 years.) and 20 age- and sex-matched healthy control subjects. Furthermore, interictal ^{123}I- iomazenil (IMZ) single photon emission computed tomography(SPECT) was examined in two of the four patients.

Among 4 patients with 22q11.2 deletion syndrome, 2 patients showed polymicrogyria and 1 patient showed agyria. Those patients with brain malformations also showed abnormal brain artery and decreased accumulation of IMZ in ^{123}I-IMZ SPECT. Although all 4 patients showed epileptic discharges in electroencephalogram(EEG), one patient with polymicrogyria had no seizure episode. Decreases in γ -aminobutyric acid(GABA) corresponding to the areas of polymicrogyria and/or epileptic discharges in EEG were shown in all patients except for the patient with agyria.

Although consistent evidence was not seen in patients with 22q11.2 deletion syndrome in this study, brain malformations and disturbances of the GABAergic nervous system would be underlying mechanisms of the neurodevelopmental abnormalities in this syndrome.

Key words

22q11.2 deletion syndrome, epilepsy, brain malformation, polymicrogyria, agyria, ^{1}H-MRS, ^{123}I-iomazenil SPECT

・Introduction

Chromosome 22q11.2 deletion syndrome is seen in 1 in 4000 to 1 in 5000 children. Individuals with 22q11.2 deletion syndrome are characterized by a considerable variety of clinical manifestations, including congenital heart disease (74%)[18], palatal abnormalities (69%)[19], characteristic facial features (hooded eyelids, a prominent nasal root with a bulbous nasal tip, hypoplastic alae nasae, and auricular abnormalities) [20]. Seventy-seven percent of individuals have an immune deficiency regardless of their clinical presentation [29]. Additional findings include hypocalcemia (9%), renal anomalies (11.6%), and skeletal abnormalities (9.3%)[1].

Although patients with this syndrome show either of the deletion sizes with 1.5-Mb or 3-Mb, their phenotypic features are not different by the different deletion sizes [32] . Nucleotide alterations of *TBX1* have been found in individuals with mimicking clinical phenotype with 22q11.2 deletion syndrome but no chromosomal deletion of 22q11.2 [32]. Therefore, *TBX1* is considered as a major genetic determinant for some of the phenotypic features of 22q11.2 deletion syndrome. Some other genes included in the deletion region would contribute to the phenotype.

In 22q11.2 deletion syndrome, many neurologic abnormalities have been identified (e.g., developmental delay in infancy 75% , behavioral or psychiatric problems 9-50%, attention deficit hyperactivity disorder 25%, schizophrenia 6-30%, and speech delay 79-84%) [14]. However, the complication of epilepsy including recurrent, apparently unprovoked seizures is not well known. Kao et al, investigated 348 patients with 22q11.2 deletion syndrome at the Children's Hospital of Philadelphia, 27 patients (7%) had apparently unprovoked seizures [12]. This is much greater than estimates in the literature of the prevalence of epilepsy in children up to age 20 years, which range between 2.8 and 20.7 per 1,000.[8]. Kao et al, also investigated the possibility that the occurrence of unprovoked seizures was secondary to effects of cardiac disease, family history of epilepsy, or prematurity, but none of these were significant risk factors for development of unprovoked seizures in individuals with a 22q11.2 deletion syndrome.

In patients with 22q11.2 deletion syndrome, polymicrogyria has been the most frequently reported brain malformation on MRI. But the other brain malformations have also been described with 22q11.2 deletion syndrome such as corpus callosum, cerebellar atrophy.[26] Since the functional characteristics of the brain lesions and epileptogenesis in 22q11.2 deletion syndrome are not yet well established, examinations using functional imaging were performed in this study.

・Patients and Methods

Patients

Four patients with 22q11.2 deletion syndrome (2 boys and 2 girls: 2~6 years old) were included in the subjects of this study.

The control subjects for ^{1}H- magnetic resonance spectroscopy(MRS) consisted of 20 age and sex matched healthy control subjects(10 boys and 10 girls, 2-6 years). The control subjects complained of nonspecific temporal symptoms, such as headache, but showed no neurologic findings and no anatomical abnormalities by magnetic resonance imaging(MRI).

Clinical informations of the patients are summarized in Table1. The three of four patients suffered from epilepsy when the study was performed, and were receiving antiepileptic drugs.

Methods

Brain MRI and ^{1}H-MRS using a clinical 3-tesla MR imager were performed. All subjects were treated with triclofos sodium (Tricloryl; 0.5 ml/kg body weight) for sedation one hour before MR examination. All measurements were performed with a clinical 3-tesla MR imager (Signa 3T HD, GE Medical Systems, Milwaukee, WI, USA) using a standard quadrature head coil for MRI, magnetic resonance angiography (MRA) and ^{1}H-MRS measurements. The criteria for hypoplasia of the intracranial artery at our institution are the existence of more than 50% partial laterality of vascular diameters and clear laterality of the degree of the depiction of peripheral vessels. For ^{1}H-MRS, in the control subjects, by using a three-dimensional image, an axial image approximately 5mm above the upper end of the corpus callosum was selected, and the center of a voxel was positioned in the left inferior frontal gyrus and the posterior margin of a voxel was placed ahead of the central sulcus. Metabolite concentrations in normal controls are described in Table2.

In the patients with 22q11.2 deletion syndrome, a single voxel was set on the image of a cortical dysplasia lesion of the inferior frontal gyrus. Furthermore, another voxel was set on the contralateral normal-appearing brain region.

MEGA was incorporated into Point Resolved Spectroscopy (PRESS) consistent with the protocol established in previous reports [21,22]. Water suppression was carried out using conventional three chemical shift-selective (CHESS) pulses after manual optimization, and was achieved at a level of less than 1%. Gradient map shimming was conducted in the measurement location by the high-order shim program, and the full width at half maximum of the water peak was less than 7 Hz. The sequence parameters were as follows: repetition time(TR) = 2500 ms, echo time(TE) = 68 ms, region of interest (ROI) = 2.5×2.5×2.5cm^{3} (15.6 ml), summation = 128 signals for each spectrum, total acquisition time = 12 minutes. Measurements with and without frequency-selective pulses were conducted alternatively, i.e., J evolution for GABA was refocused during odd-numbered acquisitions, and was not refocused during even-numbered acquisitions. Phase correction was conducted for each spectrum. Differences in the acquired spectra provided an edited spectrum for GABA. The in vitro data for N-acetyl aspartate (NAA), glutamate (Glu), and γ -aminobutyric acid (GABA) were acquired with MEGA-PRESS with the same parameters as for human measurements and set according to the LCModel basis set. Signals in J-difference edited spectra obtained by MEGA-PRESS were analyzed by LCModel (version 6.1) with our original basis set and quantification of the GABA level was based on the

unsuppressed water signal obtained from the same voxel assuming a water content of 82%, according to previous reports [6,24]. Based on findings in previous studies [30], the T2 relaxation effects were assumed to have negligible influence on quantification, although the T1 relaxation effects were compensated for according to literature values[2,6]. The criteria for selecting reliable metabolite concentrations were based on the percent standard deviation (%SD) of the fit for each metabolite that reflected the Cramer-Rao lower bounds. Only results with a %SD <15% were included in the analysis.

The parameters of the conventional stimulated echo acquisition mode (STEAM) sequence were as follows: TR = 5000 ms, TE = 15 ms, ROI = 2.5×2.5×2.5 cm^3 (15.6 ml), total acquisition time = 6.8 minutes. Before we used LCModel, an original basis-set matched with the STEAM sequence was made from the in vitro measurements of each chemical: GABA, Glu, NAA, n-acetylaspartylglutamate, creatinine (Cr), myo-inositol (mIns), glycerophosphocholine, phosphorylcholine, glycine, taurine, glucose, lactate and macromolecules. The metabolites, NAA, choline-containing compounds (Cho), Cr, mIns, and Glu were analyzed with the use of an internal water calibration method in LCModel. The %SD value of the fit for each metabolite that reflected the Cramer-Rao lower bounds was less than 15%. The concentration of each metabolite was judged to be abnormal when the value was higher or lower than 2SD of that in the control subjects.

Two of the four patients were also examined by single photon emission computed tomography(SPECT) with ^{123}I- iomazenil (IMZ). ^{123}I-IMZ is a ligand that binds to central benzodiazepine receptor (BZR). BZR and the $GABA_A$ receptor form a complex, and therefore we can obtain information about the GABA receptor indirectly by ^{123}I-IMZ SPECT. Images were obtained 180 minutes after the administration of ^{123}I-IMZ at a dose of 167 MBq. All patients were treated with triclofos sodium (Tricloryl; 0.5 ml/kg body weight) for sedation one hour before the SPECT measurement. The SPECT measurement was conducted with a two-head gamma camera scanner (E.CAM: Toshiba, Tokyo, Japan) with a fan beam collimator, a Butterworth filter, and filtered back projection (matrix size = 64x64: voxel size = 3.4 mm).

This study was approved by the Institutional Review Board of our institution, and informed consent was obtained from the family members of all of the children.

・Results

In Patients 1-3, ^{1}H-MRS showed no remarkable changes in the concentrations of NAA, Cho, Cr, Glu or mIns, as well as no obvious lactate peak (Table 2).

Patient 1

A 3 years old boy at examination. On brain MRI (Figure 1-1), regional loss of the normal gyral pattern and a mildly thick cortex predominantly in the left frontal to parietal lobe were detected. Therefore, we diagnosed his brain malformation as polymicrogyria. On MRA (Figure 2-1), hypoplasia of the left internal carotid artery and left middle cerebral artery was detected. ^{1}H-MRS (Figure 3, Table 2) showed a decreased concentration of GABA (0.31mM) at the polymicrogyria, compared with those in normal controls and that in his contralateral frontal region, where polymicrogyria was not observed. On ^{123}I-IMZ SPECT (Figure 4a), a slight decrease in the accumulation of ^{123}I-IMZ was seen in the polymicrogyria part.

Patient 2

A 6 years old girl at examination. No abnormal findings were seen by brain MRI (Figure 1-2) or MRA (Figure 2-2). On ^{1}H-MRS (Table 2), a decrease in the concentration of GABA (0.43mM) was seen in the left frontal lobe where epileptic discharges were detected on interictal electroencephalogram(EEG), compared with those in normal controls and that in her contralateral frontal region where an EEG abnormality was not observed.

Patient 3

A 2 years old girl at examination. On brain MRI (Figure 1-3), a regional loss of the normal gyral pattern and a mildly thick cortex in the right cerebral hemisphere were detected. Therefore, we diagnosed her brain malformation as polymicrogyria. MRA (Figure 2-3) showed hypoplasia of the right middle cerebral artery and right posterior cerebral artery. ^{1}H-MRS (Table2) showed a decrease in the concentration of GABA (0.45mM) in polymicrogyria, compared with those in normal controls and that in her contralateral frontal region, where polymicrogyria was not observed.

Patient 4

A 2 years old boy at the 1st examination. On brain MRI (Figure 1-4), the surface of the bilateral frontal lobes was smooth, and we diagnosed his brain

malformation as agyria. On MRA(2-4), hypoplasia of the right middle cerebral artery was seen. By ^{1}H-MRS (Table 2), a decrease in the concentration of NAA (3.4mM) and an increase in the concentration of GABA (1.5mM) were seen in the agyria region, compared with those in normal controls. No remarkable changes were seen in the concentrations of Cho, Cr, Glu and mIns. An obvious lactate peak was not detected.

At age 3 years, brain MRI was rechecked and ^{123}I-IMZ SPECT was performed. In this second brain MRI (T1-weighted image) (Figure 4b), laminar necrosis of the right parieto-occipital lobe was noted. On ^{123}I-IMZ SPECT (Figure 4b), a complete absence of ^{123}I-IMZ accumulation was noted in the right parieto-occipital cortical necrosis. In the agyria region, a reduction in the accumulation of ^{123}I-IMZ was observed.

Discussion

In patients with 22q11.2 deletion syndrome, polymicrogyria has been the most frequently reported brain malformation other than agenesis of the corpus callosum, cerebellar atrophy and meningomyelocele [26]. There was a previous large study for 32 patients with 22q11.2 deletion syndrome associated with polymicrogyria, in which broad range of severity and frequent association with asymmetry with a striking predisposition for the right hemisphere were shown [26]. The patients with 22q11.2 deletion syndrome associated with polymicrogyria showed variable neurological findings including developmental delay, hemiplegia, seizure, pseudobulbar palsy, and muscular tonus abnormality. Thus, patients with 22q11.2 deletion syndrome associated with such atypically severe neurological findings should be evaluated by neuroradiological examinations.

The etiology of polymicrogyria in this syndrome has not been well-understood. The most attractive finding is asymmetrical occurrence between hemispheres, which may be a consequence of asymmetrical expression of the responsible genes for cortical dysgenesis [4,5,7,13,26,27,33]. Another possible and more intriguing mechanism of polymicrogyria involves hypoperfusion of the embryonic brain. Some cases of polymicrogyria were considered as the results of postmigrational insults including infections and vascular abnormalities [4,7].

Haploinsufficiency of *TBX1* results in a spectrum of distinct vascular and heart defects in both mouse and human that affect the formation and growth of pharyngeal arch arteries and related structures [17,32]. In the present study, MRA revealed hypoplasia of the intracranial artery on the ipsilateral side of polymicrogyria in patient 1 and 3. This evidence suggested that polymicrogyria would be the consequence of vascular dysgenesis in these patients.

Epileptic seizures are considered to be a consequence of the relative imbalance between excitatory and inhibitory neurotransmission [9], which would precipitate hyperexcitability and an abnormally reduced concentration of GABA. Increased glutamatergic projection from the polymicrogyria to surrounding areas, which forms an extensive excitatory network, has been assumed to exist in epileptogenesis in this condition. Studies in laboratory animals have shown increases in postsynaptic Glu(excitatory) receptors and decreases in $GABA_A$ (inhibitory) receptors in the polymicrogyria cortex [10], and these changes likely promote epileptogenesis.

Previously, ^{123}I-IMZ SPECT showed low accumulations corresponding to epileptogenic foci associated with focal cortical dysplasia and temporal lobe epilepsy

[23]. In this study, ^{123}I-IMZ SPECT in patient 1 showed a low accumulation of IMZ in the polymicrogyria region, which may indicate that epileptogenesis in patients with 22q11.2 deletion syndrome was caused by decreased inhibition secondary to a decrease in GABA receptor in dysplastic cortex.

Regarding the results of ^{1}H-MRS, some controversial findings of polymicrogyria have been reported [15,16,28,31]. In a previous ^{1}H-MRS study in three patients with polymicrogyria, two showed low NAA within the lesion and two showed low NAA or a low NAA/Cr ratio in the peri-regional area [31]. An in vivo ^{1}H-MRS study for cortical malformation including polymicrogyria and heterotopia showed elevated Glu and reduced NAA levels in subjects with cortical malformation [28]. The ratio of GABA or GABA +homocarnosine/Cr was also shown to be elevated [28]. In contrast, some reports have noted a negative correlation between MRS and polymicrogyria tissues [15, 16]. In any case, there has been no report that GABA was decreased in polymicrogyria.

To date, no study has used ^{1}H-MRS in patients with 22q11.2 deletion syndrome. In the present study, we identified a reduction in the GABA concentration on the ipsilateral side of the polymicrogyria and spike discharges in patients with 22q11.2 deletion syndrome associated with polymicrogyria (patients 1 and 3). In contrast, we found no significant changes in the concentrations of NAA, Cr, Cho, mIns, or Glu in the same patients. We also found a reduction in the GABA concentration on the ipsilateral side of the spike discharges in patient 2, who had no apparent brain malformation. We thought that there may be heterogeneous pathomechanisms of epilepsy in polymicrogyria. In patients with 22q11.2 deletion syndrome, this suggests that GABAergic neurons may have been more vulnerable than glutamatergic neurons, which may be caused by insufficient fetal circulation due to vascular malformations.

To the best of our knowledge, this is the first report of a patient with 22q11.2 deletion syndrome associated with agyria(patient 4). Previously, significant reduction of NAA was identified in four patients with agyria (lissencephaly)[10], which might indicate abnormalities of neurons with either of decreased numbers, immaturity, and dysfunction. The same result was shown in the present study for the patient with 22q11.2 deletion syndrome associated with agyria.

Additionally, as the first evidence of this type in a patient with agyria, a significant increase in GABA was identified in this patient. A decreased or defective population of GABAergic neurons has been neuropathologically proven in lissencephaly due to defects in the DCX and ARX genes.[25]. The neuropathological futures and the mechanism of the increased GABA concentration in our patient with agyria(patient 4)

are unknown. There is a possibility that a significant increase in GABA on ^{1}H-MRS might be the consequence of compensation for decrease in GABA(A) receptors, since a significant decrease in IMZ binding was identified by ^{123}I-IMZ SPECT. The brain MRI findings in patient 4 with agyria were quite different from those in the other three patients. Therefore, we need to consider the possibility that the cause of cortex dysplasia in patient 4 may be different from those in the other patients.

Patient 4 was administrated clobazam, and therefore we could not exclude the possibility that clobazam affected the accumulation of IMZ in this patient. However, we thought that the degree of this decrease in IMZ accumulation was clear and greater than the possible effect of clobazam.

The cause of the parieto-occipital lobe destructive change in the MRI at 3 years in patient 4 was not clear, but the increase in the clonic convulsion of the left upper and lower limbs was observed just before the onset of this change by MRI. Only patient 4 did not undergo a radical operation for heart disease (TOF), and therefore this patient may have experienced a frequent and persistent cyanotic attack. Since the right parieto-occipital lobe was a site of vascular hypoplasia, we thought that cerebral ischemia due to the cyanotic attack may have caused this change in the image.

Despite the limited number of patients sample available for this study, the decreased concentration of GABA was demonstrated by ^{1}H-MRS in patients with 22q11.2 deletion syndrome, except for a patient with agyria, and the decreased GABA receptors were revealed by ^{123}I-IMZ SPECT in two patients with 22q11.2 deletion syndrome. Although consistent evidence was not seen in patients with 22q11.2 deletion syndrome in this study, brain malformations and disturbances of the GABAergic nervous system would be underlying mechanisms of the neurodevelopmental abnormalities in this syndrome.

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Table 1 Clinical data for subjects with 22q11.2 deletion syndrome

Patient No. Age Gender	Seizure onset age	Seizure pattern	Neurological status	Epileptiform activity on interictal EEG	Brain MRI	Brain MRA	AED	CHD
1 3 years Male	2 years	Partial seizure	Rt. Hemiparesis developmental delay(IQ 62, Tanaka-Binet test).	Spikes predominantly in the left frontal lobe	Polymicrogyria (left frontal to parietal lobe)	Artery hypoplasia (Lt arteria carotis interna, Lt middle cerebral artery)	CBZ	TOF
2 6 years Female	7 months	Apnea attack with right ocular deviation	Normal development (IQ 80, Tanaka-Binet test)	Spikes in the left frontal lobe	No abnormal finding	No abnormal finding	PB	TOF
3 2 years Female	No seizure	No seizure	Lt. hemiparesis developmental delay (DQ 41, Tumori developmental inventory)	Spikes in the right frontal lobe	Polymicrogyria (right cerebral hemisphere)	Artery hypoplasia (Rt middle cerebral artery, Rt posterior cerebral artery)	No drug	TOF
4 3 years Male	2 months	CPS (Apnea , cessation of movement)	severe developmental delay (couldn't speak any words, or perform any movement against gravity).	sharp waves frequently detected in the bilateral frontal lobes	Agyria (bilateral frontal lobes)	Artery hypoplasia (Rt middle cerebral artery)	PB, CLB	TOF, PDA, PA

AED: antiepileptic drug, CBZ: carbamazepine, CHD: congenital heart disease, CLB: clobazam, CPS: complex partial seizure, DQ: development quotient, IQ: intelligence quotient, PA: pulmonary atresia PB: phenobarbital, PDA: patent ductus arteriosus, TOF: tetralogy of Fallot

Table 2

Comparison of metabolite concentrations in the affected cortex, unaffected cortex in the same patient, and normal controls by ^{1}H-MRS.

#: The concentration of each metabolite was higher or lower than 2SD of that in the control subjects.

	Region	NAA	Cr	Cho	mIns	Glu	GABA
Patient 1	Left Frontal (Polymicrogyria)	5.4	4.1	1.2	3.6	6.8	#0.31
	Right Frontal	5.2	3.9	1.3	2.8	6.3	0.91
Patient 2	Left Frontal (side with abnormal EEGfindings)	5.8	4.0	1.2	2.5	7.4	#0.43
	Right Frontal	5.6	3.9	1.1	3.1	8.9	0.70
Patient 3	Right Frontal (Polymicrogyria)	4.6	3.6	1.3	2.8	6.8	#0.45
	Left Frontal	6.1	4.5	1.5	2.4	8.4	0.69
Patient 4	Frontal (agyria)	#3.4	3.0	1.4	3.5	6.0	#1.50
Normal Controls (n=20)	Left frontal (mean±SD)	5.4± 0.6	4.8± 0.6	1.4± 0.2	4.4± 1.1	8.0± 1.0	0.72± 0.13

・Figure legend

Figure 1. Brain MRI(T2-weighted image):

The square shows the region of interest in ^{1}H-MRS. Rt:right, Lt:left.

1. Patient 1 :Regional loss of the normal gyral pattern and a mildly thick cortex predominantly in the left frontal to parietal lobe were detected. Therefore, we gave a diagnosis of polymicrogyria.
2. Patient 2: No remarkable change was found.
3. Patient 3: Regional loss of the normal gyral pattern and a mildly thick cortex in the right cerebral hemisphere were detected. Therefore, we gave a diagnosis of polymicrogyria.
4. Patient 4: The surface of the bilateral frontal lobes was smooth, and therefore we gave a diagnosis of agyria.

Figure 2. magnetic resonance angiography (MRA)

Rt:right, Lt:left.

1. Patient 1: Hypoplasia of the left arteria carotis interna and left middle cerebral artery was detected.
2. Patient 2: No remarkable change was found.
3. Patient 3: Hypoplasia of the right middle cerebral artery and right posterior cerebral artery was detected.
4. Patient 4: Hypoplasia of the right middle cerebral artery was seen. (→: region of hypoplasia)

Figure 3. ^{1}H-MRS (Patient 1)

STEAM method(upper spectra): No remarkable change was found in the bilateral frontal lobes.

MEGA-PRESS method(lower spectra): A decrease in the concentration of GABA (0.31mM) in polymicrogyria was seen, compared with those in normal controls and that in the contralateral right frontal region of this patient, where polymicrogyria was not observed.

Figure 4 ^{123}I-IMZ SPECT and Brain MRI

Rt:right, Lt:left.

a ：Patient 1

^{123}I-IMZ SPECT：A slight decrease in the accumulation of ^{123}I-IMZ was seen in the polymicrogyria region. (arrow)

b ：Patient 4

Results of the second brain MRI (age 3 years, T1-weighted image)： Laminar necrosis of the right parietal and occipital lobes was seen.

^{123}I-IMZ SPECT (age 3 years)： A complete absence of the accumulation of ^{123}I-IMZ was seen in the right parietal and occipital cortical necrosis.(arrowhead) In the agyria region, the accumulation of ^{123}I-IMZ was reduced.(arrow)

Fig.1

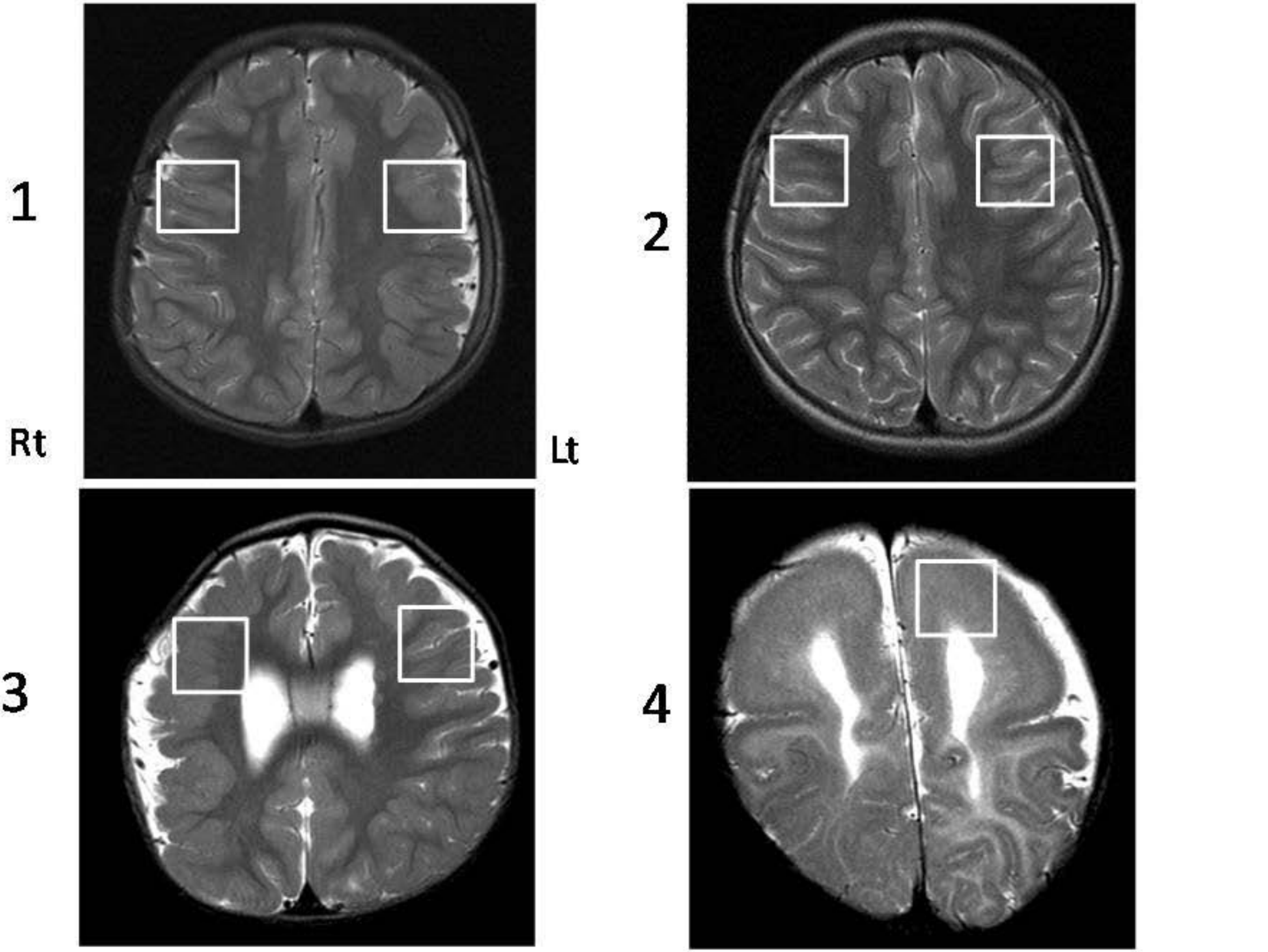
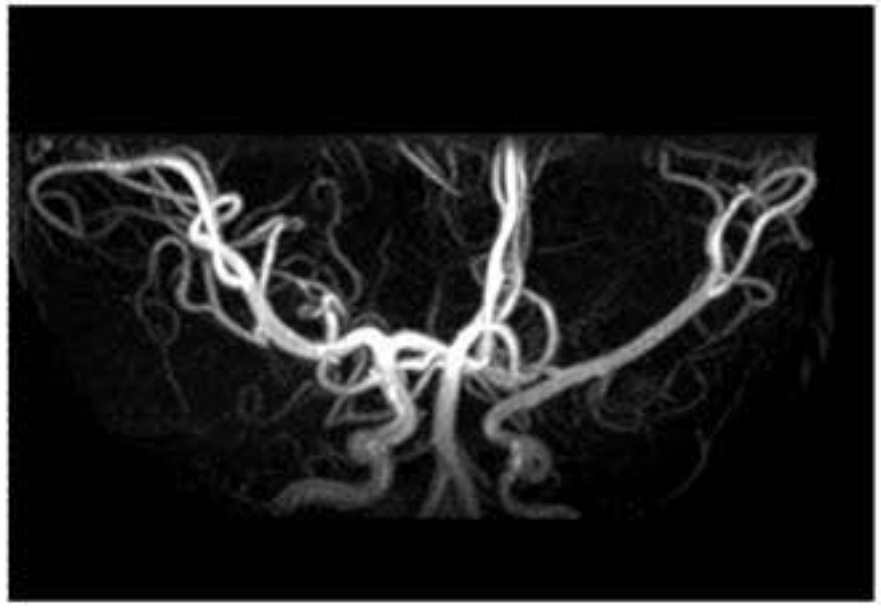


Fig.2

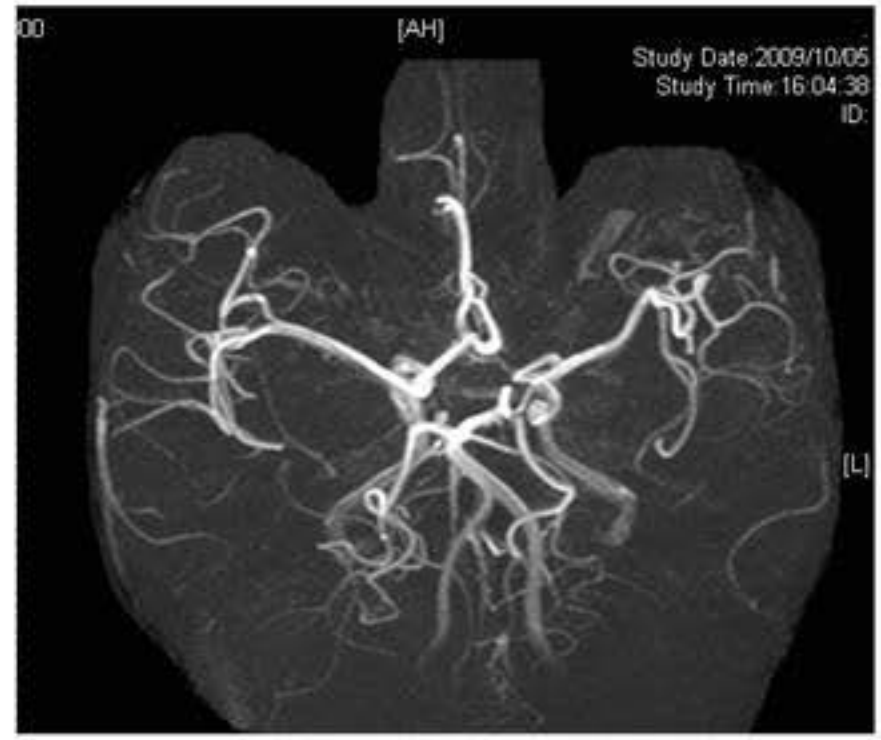
1



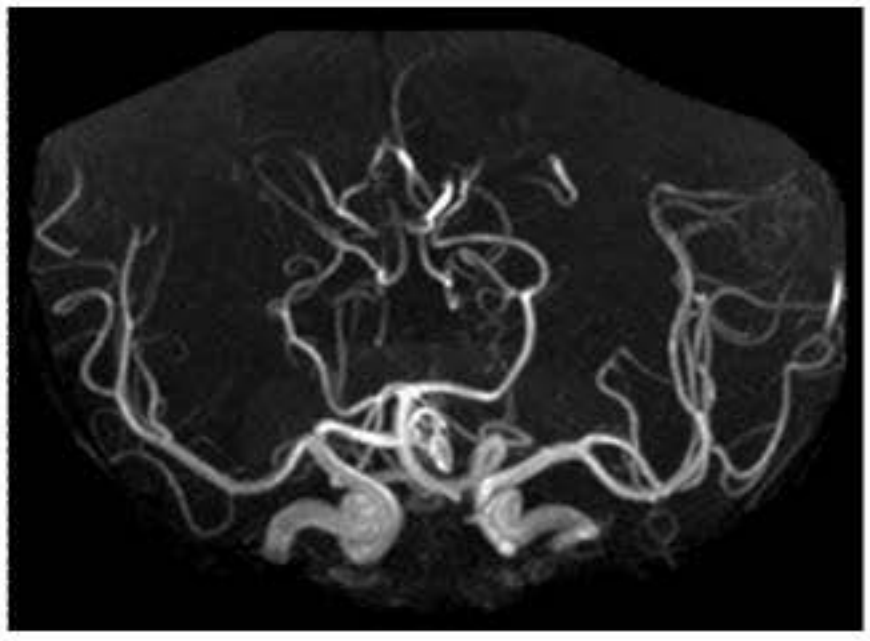
Rt

Lt

2



3



4

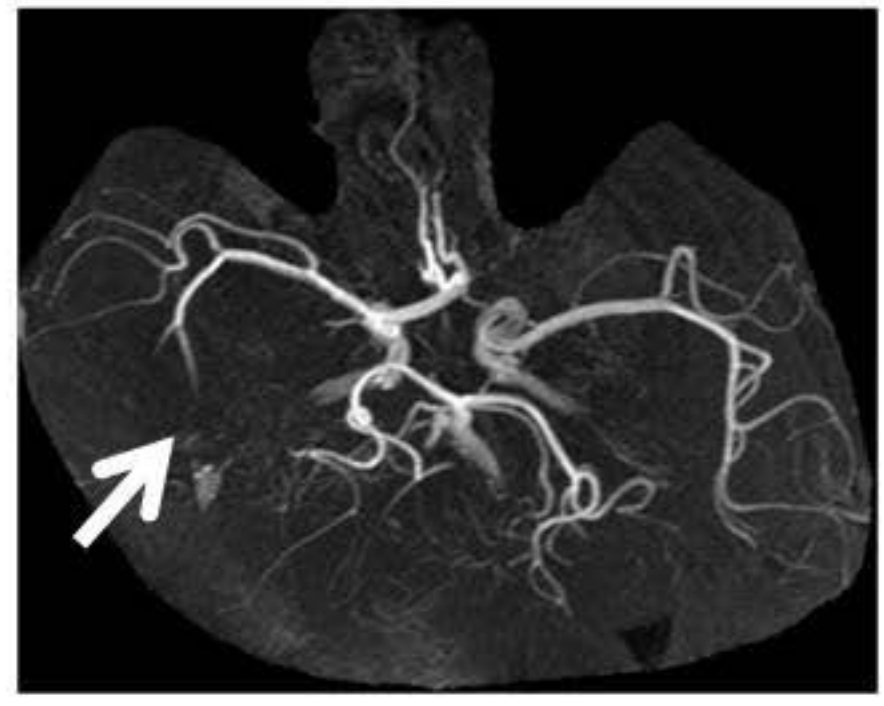
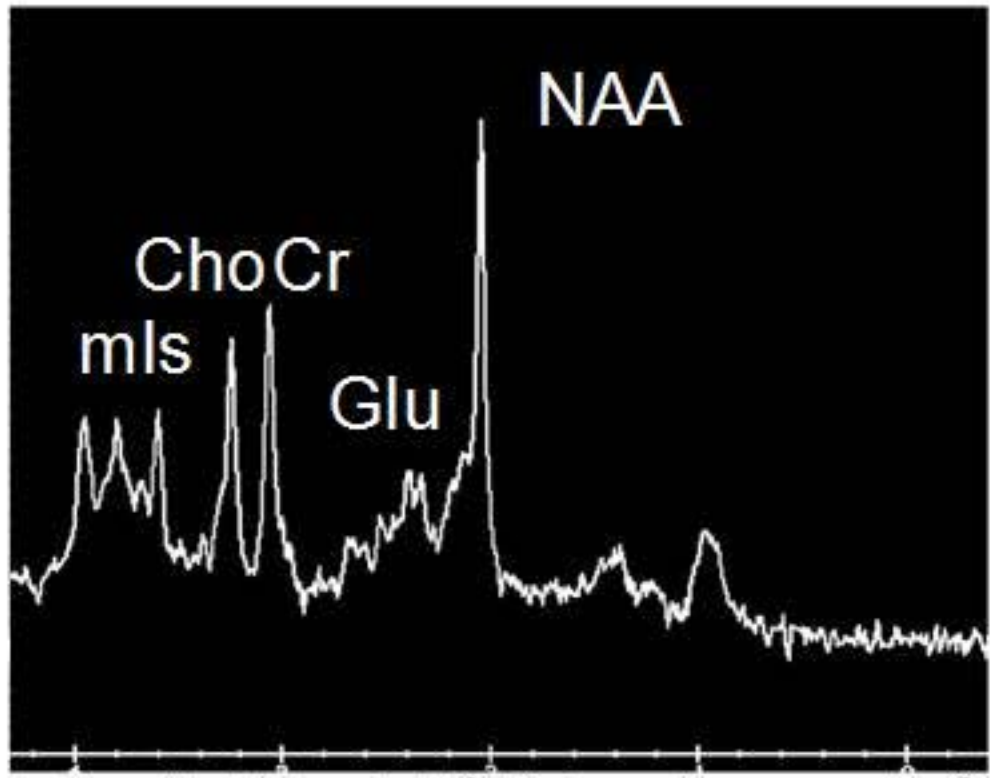
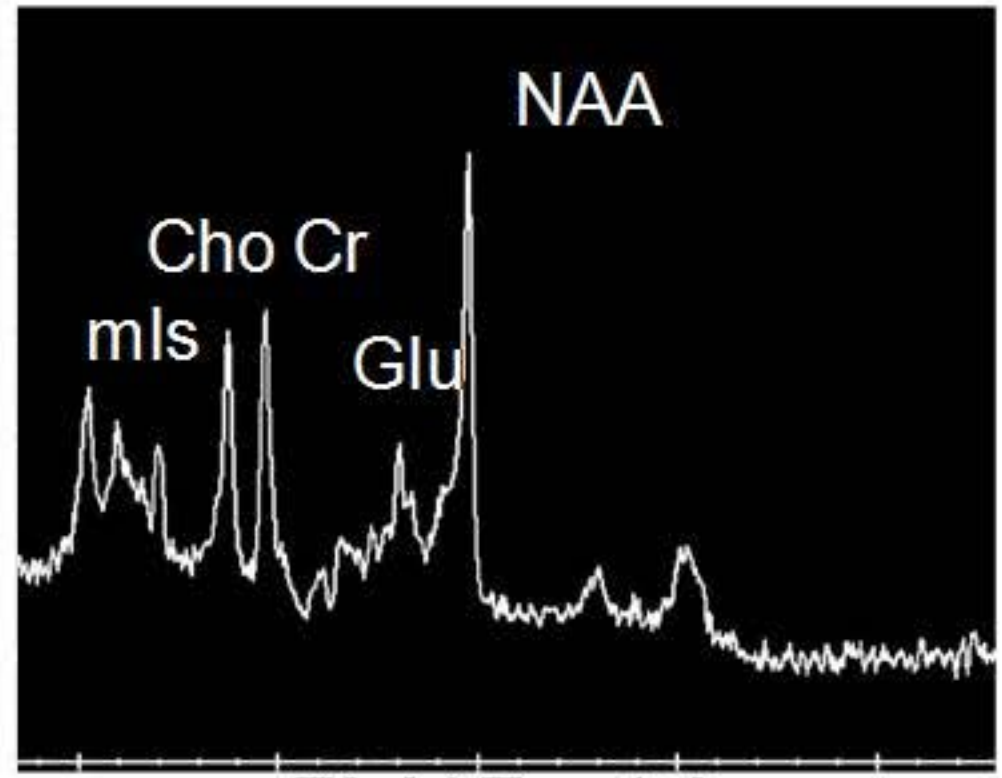


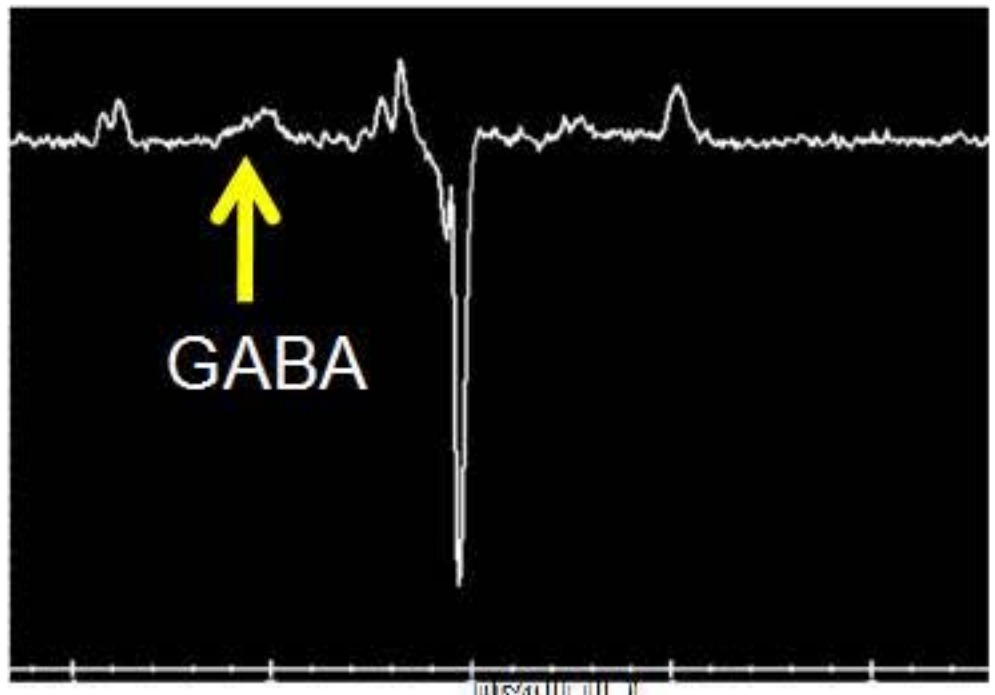
Fig.3



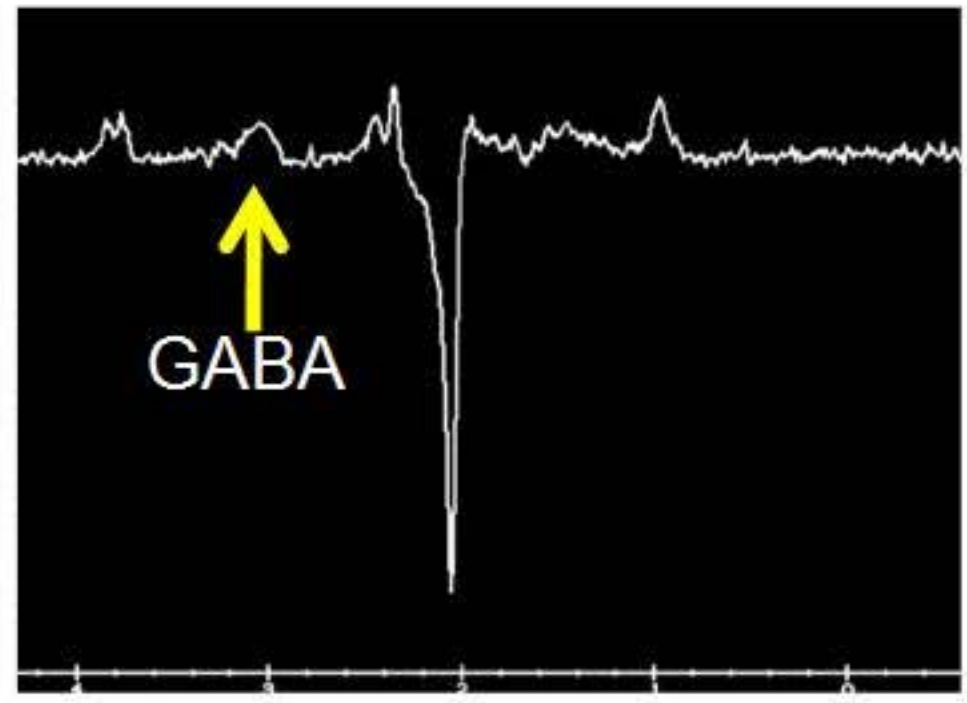
Left Frontal (Polymicrogyria)



Right Frontal



Left Frontal (Polymicrogyria)



Right Frontal

Fig.4